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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/679,951	**Applicant(s)** LUTHER ET AL.	
	Examiner Zachary C. Howard	**Art Unit** 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2006*.
2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-42,45-53,55-59 and 61* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *39-42,45-53,55-59,61* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on *22 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☒ All b)☐ Some * c)☐ None of:
1.☒ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 6/22/06 has been entered in full. Claims 39, 45, 46, 49, 50 and 56 are amended. Claims 1-38, 43, 44, 54 and 60 are canceled.

Claims 39-42, 45-53, 55-59 and 61 are under consideration in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (2/22/2006).

The objection to the drawings at pg 2-3 is *withdrawn* in view of Applicants' submission of amended drawings.

The objection to the specification at pg 3 is *withdrawn* in view of Applicants' amendments to the specification.

All rejections of claims 43, 44, 54 and 60 are moot in view of Applicants' cancellation of these claims.

The rejection of claims 50-53 and 55 under 35 U.S.C § 112, second paragraph, at pg 7-9 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 39-42, 45-49, 56-59 and 61 under 35 U.S.C § 112, second paragraph, at pg 7-9 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn in part* in view of Applicants' amendments to the claims. Please see the section "Claim Rejections – 35 USC 112, 2nd paragraph" below for the maintained rejection of these claims.

The rejection of claims 39, 45 and 49 under 35 U.S.C. § 102(b) at pg 9-10 as being clearly anticipated by Casey et al (1994) is *withdrawn* in view of Applicants' amendments to the claims.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

Claims 39-42, 45-53, 55-59 and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of providing a prognosis for a breast-cancer patient comprising measuring the ratio of uPAR del4+5 deletion variant to del2+3+4, does not reasonably provide enablement for a (1) a method for the detection of tumors associated with generation of uPAR deletion variants; (2) a method of predicting the risk of cancer in a tumor-bearing patient; (3) or a method of providing prognosis for a tumor-bearing patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection was set forth at pg 3-7 of the 2/22/06 Office Action.

The Examiner has fully considered all of Applicant's arguments in the 6/22/06 response. The Examiner finds persuasive Applicants' arguments (at pg 15, line 13 to pg 17, line 5) in response to the passages from Kotsch (2005) cited by the Examiner at pg 4-5 of the 2/22/06 Office Action. However, the rejection of the claims is maintained for the reasons set forth previously at pg 5-7 of the 2/22/06 Office Action and reiterated herein. The Examiner addresses Applicants' remaining arguments below.

The claimed invention encompasses methods based on the detection of splice variants of the urokinase-type plasminogen activator receptor (uPAR). The specification identifies two novel uPAR splice variants (del4 and del4+5); a third was known previously in the art (del5). Each variant is the result of an alternative splicing event that removes exon 4 and/or exon 5 from the mRNA encoding the uPAR protein. Applicants have associated a "high del4+5 versus del2+3+4 ratio with a high relapse frequency (Fig 21)" (see specification, pg 29, lines 20-21). The sample termed "del2+3+4" includes any variant with exon 2, 3, and 4 and therefore includes both wild type uPAR (also termed del-wt) and the variant del5. The high relapse frequency was observed in patients afflicted with primary breast cancer. In view of Applicants' working example, the claims are enabled for a method of providing a prognosis comprising obtaining a breast cancer sample by measuring the ratio of del4+5 cDNA versus del2+3+4 cDNA, wherein patients with a high ratio have a high relapse frequency. However, this single working example does not provide enablement for the full scope of methods encompassed by Applicants' claims for the following reasons:

(1) Applicants' claimed methods encompass a method of prognosis for any form of tumor or cancer. Applicants have provided prognosis for a single type of cancer (breast cancer) based on a single comparison of relative transcript levels. This is not sufficient to enable a broad genus of cancers. This was set forth at pg 5-6 of the 2/22/06 Office Action. In the 6/22/06 response at pg 17, Applicants argue that the association of uPAR deletion variant levels with tumors is predictable. Applicants further argue that Kotsch (2005) states that del4+5 variant expression leads to a high prognostic value in tumor diseases and does not indicate that this value is limited to a specific type of cancer, even though the study was performed only with breast cancer.

Applicants' arguments have been fully considered but are not found persuasive. Kotsch is silent as to the applicability of the prognostic value of the del4+5 variant in other cancer tissues. However, it is well known in the art that splice variant expression "patterns of alternative splicing can be tissue, stimulus or disease specific" (see pg 586 of Brinkman et al. 2004. Clinical Biochemistry. 37: 584-594). Further, Kalnina et al (2005) teaches, "The selection of alternative splice sites can be regulated in different manners: tissue specificity, developmental stage, physiological processes, sex determination, and in response to various stress factors" (pg 344 of Kalnina et al. 2005. Genes, Chromosomes and Cancer. 42: 342-357). Furthermore, alternative splicing is frequently tumor-specific; Okumura et al (2005) found that "among these 31 examples, 21 showed apparent differences between the normal and tumor alternative splicing patterns in at least one tissue, with six showing a difference in all four tumor tissues examined (Table 1) (see pg 24 of Okumura et al. 2005. Biochemical and Biophysical Research Communictions. 334: 23-29). Therefore, as set forth previously, it is unpredictable whether or not results similar to those found by Applicants for del4+5 in breast cancer would be found with other types of cancer. To enable the use of the claimed method for prognostic generalizations for all cancer, one of skill in the art would first need to engage in undue experimentation to determine whether or not expression of the del4+5 splice variant is correlated with cancer prognosis in a variety of cancer types.

(2) Applicants' claimed methods encompass diagnosis and prognosis by detection of any uPAR deletion variant, wherein at least one uPAR deletion variant is del4, del5 or del4+5. However, Applicants have only provided a single working example consisting of a single type of analysis wherein a particular ratio (del 4+5 cDNA versus del 2+3+4 cDNA) is correlated with a particular prognosis for a particular cancer (breast). This is not sufficient to enable the method with the genus of deletion variants including del4, del5 or del4+5. This was set forth at pg 6 of the 2/22/06 Office Action.

Applicants' response does not appear to specifically address the issue of using uPAR deletion variants such as del4 or del5 for diagnosis or prognosis. Applicants argue generally that they have demonstrated that "measuring single variants of uPAR with a specific assay leads to a prognostic relevance and a clear, uniform conclusion".

Applicants' arguments have been fully considered but are not found persuasive. Claims 39-42 and 45-49 encompass a method of determining the ratio of uPAR del4 or del5 cDNA to wild type uPAR cDNA. Claims 50-53 and 55 encompass a method of determining the risk of cancer in a tumor-bearing patient based on the presence of a del4 or del5 deletion variant. Claims 56-59 and 60 encompass a method of determining a prognosis for a tumor-bearing patient based on the presence of a del4 or del5 deletion variant. However, Applicants have not identified any diagnosis or prognosis that is associated with the presence of del4 or del5 deletion variant, or is associated with ratio of del4 or del5 to the wild type isoform (del-wt). Furthermore, Applicants' results with del4+5 do not address the predictability of using del4 or del5 in methods of diagnosis or prognosis of cancer. These deletion variants are expressed at different levels in breast cancer samples; in 205 samples the median level of expression the variant del5 was different than the median level of expression of del4+5 (see pg2762-2763 of Kotsch, 2005). Further, Kotsch (2005) teaches that "[t]he expression levels of uPAR-wt and uPAR-del5 were not associated with prognosis" (pg 2763 and pg 2767). No teachings are available regarding the expression levels of a del4 splice variant and the Examiner can find no teachings that such a splice variant is actually produced in normal or tumor tissues. It is unpredictable whether or not the expression of del4 or del5 can be used to diagnose or prognose cancer.

The 2/22/06 Office Action further stated that claims 40, 41, 51, 52, 57, and 58 specifically recite "uPAR deletion variant or a fragment thereof" and/or "wild type uPAR or a fragment thereof", and the remaining claims encompass said fragments. However, the specification does not teach any fragments of wild type uPAR or fragments of uPAR splice variants.

In response, Applicants argue that the claims reciting the term "fragments" are enabled in view of the specific teachings and full context of the specification. Applicants assert that the specification teaches features of fragments and how to obtain and use said fragments in accordance with the invention. Applicants point to pg 5, lines 4-8 as teaching that fragments encompass sequences with a minimum of six amino acids and deletion variants different from complete uPAR sequences.

Applicants' arguments have been fully considered but are not found persuasive. While the specification may state that fragments of del4, del5, or del4+5 as small as six amino acids can be used in the claimed invention, this does not provide any guidance as to whether or not any particular fragment actually exist that can be used detection or prognosis of tumors. The del4, del5, del4+5 proteins consist of sequences of over one hundred amino acids, and therefore the genus of fragments encompassed by the claims includes hundreds of fragments wherein one or more amino acids from the sequence of del4, del5 or del4+5 is deleted. It is unpredictable whether or not any fragments of del4, del5, or del4+5 exist that can be used in the claimed methods. Furthermore, even if such fragments exist, their nature is unpredictable. Applicants have provided no guidance as to the nature of fragments that are correlated with risk of cancer or disease-free prognosis. What Applicants have provided is a mere wish or plan and an invitation to experiment.

(3) Claims 50-53 and 55 are directed to methods of predicting the risk of cancer in a tumor-bearing patient; i.e. determining the risk of a tumor being malignant as opposed to benign. Applicants have provided no working examples showing that detection of an uPAR deletion variant can discriminate between benign and malignant tumors. In the 6/22/06 response, Applicants argue that the specification does address discrimination between benign and malignant tumors. Applicants point to the Example (starting at pg 16) in the specification that provides a comparison between malignant and non-malignant cells and reveals that deletions were not found in the non-malignant cells.

Applicants' arguments have been fully considered but are not found persuasive. Claims 50-53 and 55 are directed to a method for distinguishing between malignant and non-malignant tumors, based on analysis of a sample of a tumor from a patient. However, Applicants' examples demonstrate analysis of uPAR splice variants in a single non-malignant type of cell (polymorphonuclear neutrophils prepared from blood; Figure 16, lane "PMN") and six cancer cell lines (Figure 16 and Figure 17). Applicants do not provide any information on the expression of the deletion variant in healthy matched tissue (e.g., healthy matched breast tissue) or in non-malignant tumor (e.g., benign breast tumor). With respect to breast cancer, the relevant art teaches, "There are many types of benign lesions in the human breast and only a few appear to have significant premalignant potential" (pg 47 of Allred et al, 2001. Endocrine-Related Cancer. 8: 47-61). Therefore, there is no basis to predict whether or not a patient with a tumor having the splice variants is at a higher risk of developing cancer than one not having the splice variants. One of skill in the art would need to engage in undue experimentation in order to examine splice variants from tumor samples of patients and determine whether a correlation exists between splice variant expression and development of cancer (versus non-development in the case of a benign tumor).

For these reasons it is maintained that while the level of skill of those in the art is high, it is not disclosed and not predictable from the limited teachings of the prior art and specification whether the claimed methods of the present invention could be used for the full scope of the claims. The breadth of the claims is such that the claims encompass a large number of variables (types of cancer, types of deletion variants and fragments of such, and diagnosis as compared to prognosis of known malignant tumors) for which it is unpredictable whether or not the claimed method will work. Therefore, the specification fails to teach the skilled artisan how to use the full scope of the claimed methods without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the claimed methods for the above stated purpose.

Due to the large quantity of experimentation necessary to determine if claimed methods of the present invention could be used to diagnose or prognose any type of cancer (other than with the single working example provided in the specification) with measurement of any single or multiple measurements of any uPAR deletion variant, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicants have provided is a mere wish or plan and an invitation to experiment.

Claim Rejections - 35 USC § 112, 2nd paragraph

Claims 39-42, 45-49, 56-59 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the response dated 6/2206, Applicants state, "In response, Applicants have amended the claims, as appropriate, to address the Examiner's concerns" and

"Applicants believe that all of the Examiner's rejections under 35 U.S.C. § 112, second paragraph, have been fully overcome" (pg 18-19).

Applicants' arguments have been fully considered but are not found persuasive. Applicants' claim amendments do not address several basis for rejection of the claims under 35 U.S.C. § 112. These were set forth previously and are reiterated herein.

Claim 39 is indefinite because it is unclear how analyzing the cDNA of the tumor sample leads to the identification required the preamble – "detection of tumors associated with the generation of at least one uPAR deletion variant". Clarity could be added to the claim by adding at the end a phrase such as, "wherein the presence of at least one uPAR deletion variant in said tumor indicates the presence of a tumor associated with the generation of at least one uPAR deletion variant." Note that there must be basis in the specification for the type of response and the suggestions made by the examiner do not necessarily have basis but are intended to present the general idea of concepts that may be suitable. This rejection was set forth at pg 7-8 of the 2/22/06 Office Action; Applicants response and claim amendments do not address this rejection.

Claim 45 is also indefinite because it recites the goal "wherein the method provides a prognosis for tumors associated with the generation of at least one uPAR deletion variant", but there is no indication of how this goal will be met by the claimed method. What prognosis is provided if a uPAR deletion variant is generated? This rejection was set forth at pg 8 of the 2/22/06 Office Action; Applicants response and claim amendments do not address this rejection.

Claim 56 is indefinite because it is unclear how a prognosis will be provided for a tumor-bearing patient and what that prognosis will be based on the results of the detection and correlation in steps (b) and (c). It is unclear how the correlation performed in step (c) will provide the patient with a prognosis, and what that prognosis will be based on the presence or absence of a uPAR deletion variant. This rejection was set forth at pg 9 of the 2/22/06 Office Action; Applicants response and claim amendments do not address this rejection.

The remaining claims are rejected for depending from an indefinite claim.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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